(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 323 430 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
14.03.2007 Bulletin 2007/11

(51) Int Cl.:
A61K 47/10 *(2006.01)* ***A61K 47/12*** *(2006.01)*
A61K 9/06 *(2006.01)* ***A61K 31/4422*** *(2006.01)*

(21) Application number: **03003313.8**

(22) Date of filing: **03.08.2001**

(54) Composition for transdermal and/or transmucosal administration of active compounds that ensures adequate therapeutic levels

Zusammensetzung zur transdermalen und/oder transmukosalen Verabreichung von Wirkstoffen, die ausreichende therapeutische Spiegel garantiert

Composition pour l' administration percutanée et/ou par voie transmucosale de principes actifs assurant des niveaux d'efficacité thérapeutiques adéquats

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

(30) Priority: **03.08.2000 WOPCT/EP00/07533**

(43) Date of publication of application:
02.07.2003 Bulletin 2003/27

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
01960619.3 / 1 307 232

(73) Proprietor: **Antares Pharma IPL AG**
6301 Zug (CH)

(72) Inventors:
- **Carrara, Dario**
  4132 Allschwil (CH)
- **Porto, Gabriel**
  4132 Allschwil (CH)
- **Rodriguez, Jorge**
  4132 Allschwil (CH)

(74) Representative: **Gerli, Paolo**
Notarbartolo & Gervasi,
Corso di Porta Vittoria 9
20122 Milano (IT)

(56) References cited:
EP-A- 0 249 397 **US-A- 4 952 560**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 1 323 430 B1

Description

FIELD OF THE INVENTION

[0001] The present invention relates to a novel composition for transdermal administration of different active compounds or a mixture thereof. The invention reveals a pharmaceutical formulation with good cosmetic properties and low irritation potential, useful for the systemic treatment of diverse diseases by transdermal or transmucosal route. A formulation that administers the active drug (s), at a permeation rate that would ensure therapeutically effective systemic concentration, containing defined amounts of chemicals that minimize the barrier characteristics of the most uppermost layer of the epidermis and provide sustained permeation rate. Said chemicals are: fatty alcohols such as lauryl alcohol, n-decanol, oleyl alcohol, etc. and diethylene glycol monoethyl ether in a ternary vehicle composite consisting of ethanol, propylene glycol and water.

BACKGROUND OF THE INVENTION

[0002] It is well known that many drugs taken orally, are destroyed on the first pass through the liver. It is also well known that when many drugs are taken orally, their rate of absorption into the body is not constant. In view of such difficulties, a number of different drug delivery systems have been developed.

[0003] The transdermal or transmucosal route for delivery of drugs provides many advantages, and transdermal or transmucosal systems for delivering a wide variety of drugs are described in U.S. patents number 5,785,991; 4,764,381; 4,956,171; 4,863,970; 5,453,279; 4,883,660; 5,719,197 or EP patent application number 0 271 983; 0 267 617; 0 261 429; 0 526 561; as an example, some of which are mentioned hereinafter.

[0004] A major drawback of this therapy however, is the limitation of me amount of drug that can be transported across the skin, in many cases, drugs which would appear to be ideal candidates for transdermal delivery are found to have such low permeability through intact skin that they cannot be delivered in therapeutically effective amounts from transdermal devices. This limitation is due to several factors. Since the skin is a protective barrier by nature, the rates of transport of most compounds through the skin is quite slow. It is generally accepted that a surface of patch beyond 50-100 sqcm would result in difficulty of application. Therefore the application of a transdermal semisolid dosage form such as a gel, cream, ointment, liquid, etc., augments the patient's compliance and the surface of application can be extended.

[0005] In order to increase skin permeability so that drugs can be delivered in therapeutically effective amounts at therapeutically effective rates, it has been proposed different systems or devices or mechanisms one of which is deliver the drug (s) in presence of permeation enhancers. Usually, using penetration enhancing compounds, processes or devices to increase drug penetration solve this problem.

[0006] Various systems were suggested for this purpose, as described in different patents such as U.S. patents number 5,785,991; 4,764,381; 4,956,171; 4,863,970; 5,453,279; 4,883,660; 5,719,197 or W.O. patents number 97/29735; 98/17316 or in the literature "Pharmaceutical Skin Penetration Enhancement", J. Hadgraft, Marcel Dekker, Inc. 1993; "Percutaneous Absorption", R. Bronaugh, H. Maibach, Marcel Dekker, Inc. 1989, etc.

[0007] To be accepted, a permeation enhancer or a combination thereof should have the ability to enhance the permeability of the skin for the drug, should be non-toxic, non-irritant and non-sensitizing on repeated exposure.

[0008] It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs. That is also concluded after careful analysis of the scientific literature relating to this specific topics, such as "Transdermal Therapeutic Systemic Medications, Marcel Dekker Inc., New York, 1989" (see table on page 3).

[0009] Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work.

[0010] EPA 0 279 977 describes a transdermal device for administering progesterone and an estradiol ester alone or in combination, utilizing a polymer matrix which has the drug(s) with a penetration enhancer such as sucrose monococoate, glycerol monooleate, sucrose monolaurate, glycerol monolaureate, etc.

[0011] EPA 0 367 431 discloses that aliphatic alcohols such as isopropyl alcohol and isobutyl alcohol that are commonly used in topical transdermal formulation, thus, enhance the rate of transdermal delivery of steroid drugs.

[0012] WO 90/11 064 discloses a skin penetration enhancer composition for transdermally administered pharmacologically active agents. The composition contains diethylene glycol monoethyl or monomethyl ether in addition to an ester component such as propylene glycol monolaurate, methyl laurate or the like.

[0013] US 5,785,991 discloses a composition, device and method for transdermal administration of an active agent using a novel dual permeation enhancer mixture comprising lauryl acetate and a monoglyceride, glycerol monolaurate.

[0014] US 4,764,381 discloses pharmaceutical preparations comprised of a pharmaceutically active ingredient and a carrier which comprises a percutaneous penetration enhancer comprised of 2-ethyl-1,3 hexanediol alone or in combi-

nation with oleic acid.

[0015] US 4,863,970 discloses penetration-enhancing pharmaceutical compositions for topical transepidermal and percutaneous application which are non-irritating to the skin and describes a binary system of oleic acid or alcohol and a lower alcohol.

[0016] US 5,453,279 describes an enhancing transdermal absorption composition useful in transdermal absorption of progestins including progesterone and optionally an estrogen for contraceptive or HRT. The enhancing composition comprise a combination of a lower alkyl ester of a polycarboxylic acid, an aliphatic monohydroxy alcohol and an aliphatic diol.

[0017] EP 0 526 561 B1 relates to the use of chemical penetration enhancers to enhance the transdermal delivery of medicaments through the skin, said chemical enhancers are alcohols.

[0018] EP-A-249397 describes the association of minoxidil with narrowly selected C16-C18 alcohols. EP-A-13459 teaches topical antiacne compositions containing benzoyl peroxide as active agent, in a mixture with polar lipids. US-A- 4952560 discloses ointments containing a drug, a soluble proteins like gelatin, lower alkanols, alkylene glycols and optional oleogineous substances.

[0019] None of the above mentioned inventions or publications report a study of lauryl alcohol together with diethylene glycol monoethyl ether in a ternary vehicle composite in a semisolid dosage form, designed to administer transdermally or through the mucosal membrane the group of active agents mentioned in the present invention. None of the above mentioned inventions or publications describe an adequate, transdermal or transmucosal formulation to deliver therapeutic plasma levels of different types of active compounds, as it is disclosed in the present invention.

[0020] One object of the present invention is to obtain a transdermal formulation that could deliver, at controlled rates, an active compound or a mixture thereof, combined with appropriate permeation enhancers. As it is well described in the literature of the art, there is not obviousness regarding the use of penetration enhancers to administer a drug (s) by transdermal route. As it is mentioned by W. R. Pfister in its chapter on "Transdermal and Dermal Therapeutic Systems: Current Status" in "Transdermal and Topical Drug Delivery Systems", Interpharm Press Inc., Buffalo Grove Illinois, 1997, pages 33-112, no general guidelines exist that will ensure success in selecting an appropriate enhancer for a specific drug to be delivered from a transdermal device (Hsieh 1994). The science of optimizing topical formulations is not predictive from one drug to another and permeation enhancers can produce a wide range of enhancement factors across drugs having different physicochemical properties. Rather, this is a process that requires extensive experimental work.

[0021] It is also important to mention that transdermal permeability is mainly influenced by both physicochemical properties of the permeants and by the interaction of the permeants with the enhancers. Therefore a given enhancer could prove to be very adequate for a drug and simultaneously would not increase the permeability of the other compound. This is well illustrated by Chien, in its chapter on "Developmental Concepts and Practice in Transdermal Therapeutic Systems" in Transdermal Controlled Systemic Medications, Marcel Dekker Inc., New York, 1987, pages 25-81, who states that a penetration enhancer increases the permeation of different compound to different degree.

[0022] There has not been known an enhancer or combination thereof which shows the transdermal penetration enhancement effect for any active agent or drug. As an example we can quote results of this author as wherein below indicated:

Enhancement of skin permeability of various drugs by different types of enhancers				
	Enhancement factor (a)			
Drugs	Propyl myristate	Propyl oleate	Azone	Decymethyl sulfoxide
Progesterone	4.56	5.36	5.96	11.04
Estradiol	9.33	14.62	20.17	12.59
Hydrocortisone	4.57	5.01	61.3	25.23
Indomethacin	3.77	4.67	14.49	15.67
(a) Enhancement factor = (Normalized skin permeation rate) with enhancer/(Normalized skin permeation rate) without enhancer				

[0023] Additionally, another argument in favor of our position is sustained when the results reported by Chien are analyzed. He published the dependence of the enhancement factor for the skin permeation of progesterone on the alkyl chain length of saturated fatty acid in "Transdermal Controlled Systemic Medications". He found the major enhancement effect using caproic acid (C8), however the same author discloses in US patent 5,145,682 that the better enhancer for estradiol is decanoic acid (C10). These results lead us to attain the same conclusion of Chien in "Transdermal Controlled Systemic Medications", Marcel Dekker, New York 1987, pages 25-81, that concludes that the efficacy of skin penetration

enhancer for a specific active agent, is function of the type, concentration and, how the penetration enhancer release from the devices.

[0024] The prior art presented herein clearly prove that at least for some compounds, as shown in the present patent application, there is no such an universal penetration enhancer composition and the adequate permeation rate across the skin can be achieved only by testing different types of compounds at different concentrations. Although prior art was useful for the theoretical approach, the results herein disclosed emerged from the careful investigation of multiple variables.

BRIEF DESCRIPTION OF THE FIGURES

[0025]

Figure 1 represents an apparatus "Hanson P/N 57-VC (vertical diffusion cell) 3, is schematically represented wherein:

1 = cell receptor
2 = donor chamber (dosage area)
3 = top plate
4 = dosage water
5 = clamp
6 = membrane
7 = water jacket
8 = sample point
9 = stirring helix
10 = magnetic stirrer
11 = sample tube
12= sample probe from microette
13 = cell level line
14 = media replace tube

Typical cell dimensions are: orifice 15 mm, volume 7 ml.
Figure 22 represents Graphic XXI relevant to the data from Table XXX, Examples 36-39

SUMMARY OF THE INVENTION

[0026] The composition of the present invention relates to a penetration enhancing system that can be utilized in many types of products for topical or transdermal application, that include, but are not limited to, solutions, creams, lotions, sprays, ointment, gels, aerosols and patch devices.

[0027] While it is known in the art to combine permeation enhancers, this invention utilizes a novel combination of fatty alcohol (lauryl alcohol) and diethylene glycol monoalkyl ether (diethylene glycol monoethyl ether), and the combined effect is a significant and surprising improvement over use of lauryl alcohol or diethylene glycol monoethyl ether alone.

[0028] The present invention relates to a composition for topical application having penetration-enhancing properties, the composition comprising an active or a mixture thereof; and a penetration enhancing system that comprises lauryl alcohol and also diethylene glycol monoalkyl ether in combination with a complex ternary vehicle comprising purified water, a C_1-C_4 alcohol and a glycol. The composition further comprises a gelling agent and a neutralizing agent when necessary. In preferred embodiments, the gelling agent is a carbomer (Carbopol®) which is a polyacrylic acid and/or a polyoxyethylene polyoxypropylene copolymer and the neutralizing agent is an amine like triethanolamine or trometh-amine. Preservatives, flavor agents, saborizants, sweeteners any other solubilizants can be added as well.

[0029] The enhancing composition herein presented has proven to effectively enhance delivery and absorption of physiologically active substances through the skin and mucosa. That was properly demonstrated by first carrying out *in vitro* studies to evaluate its applicability to a determined active drug(s) and then to further confirm its effectiveness in *in vivo* studies in human volunteers. The penetration enhancing system of the present invention can also be used for mucosal delivery.

[0030] Hence, it has been surprisingly discovered that it is possible to achieve a therapeutically effective, sustained and controlled penetration rate of diverse active substances into the skin with the aid of the inventive means.

[0031] It has been discovered surprisingly that the formulation discloses herein, exerts higher permeation rate when is compared with a formulation without containing the invention.

[0032] It has been surprisingly discovered also that by utilizing lauryl alcohol and diethylene glycol monoethyl ether (Transcutol®P) as enhancing composition for the invention herein disclosed, an adequate penetration enhancement

factor and a sustained flux of the active agent is attained, thereafter reflected in achieving therapeutic effective, controlled and sustained levels of the active drugs by only once-a-day application of the formulation.

[0033] In another aspect, the present invention relates to a method for administering topically or systemically different active substance(s).

DETAILED DESCRIPTION OF THE INVENTION

[0034] It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs.

[0035] Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed.

[0036] An objective of this invention is to provide a formulation, which shows adequate transdermal penetration enhancement effect for different therapeutical compounds classified in different groups.

[0037] The main objective of this invention is to provide a semisolid dosage form, which shows adequate and effective transdermal penetration enhancement for different active drugs.

[0038] Accordingly, it is an object of the present invention to provide a skin permeation enhancer composition comprising of a first component that is a saturated fatty alcohol given by the formula CH_3-$(CH_2)_n$-CH_2OH, in which n is an integer from 8 to 12, most preferably 10 and also a second component that is a monoalkyl ether of diethylene glycol, preferably diethylene glycol monoethyl ether or diethylene glycol monomethyl ether, in a vehicle or carrier composition, integrated by an C_1-C_4 alkanol, preferably ethanol; a polyalcohol, preferably propylene glycol and purified water. The composition may also comprise additional components such as gelling agents, pH regulators, preservatives, flavor agents, saborizants, sweeteners, stabilizers, antioxidants, other solubilizants and the like.

[0039] The transdermal delivery system of the present invention comprises:

1. One or more active agents, or a mixture thereof The term '"drug" or "active drug" or "active agents" or "pharmaceutical active drug" as used to describe the principal active ingredient of the device intends a biologically active compound or mixture compounds that has a therapeutic, prophylactic or other beneficial pharmacological and/or physiological effect on the wearer of the device. Said drugs are selected in the group of Antihypertensives for instance Benzothiadiazine Derivatives such as Captopril, Cilazapril, Enalapril, Lisinopril, Perindopril, Ramipril; Guanidine Derivatives such as Guanethidine; Quinazoline Derivatives such as Alfuzosin; Reserpine Derivatives such as Reserpine, Sulfonamide Derivatives such as Furosemide; others such as Minoxidil, Amlodipine, Doxazosin Mesylate, Felodipine, Moxonidine, Nicardipine Hydrochloride, Nifedipine, Prazosin hydrochloride, etc and Calcium Channel Blockers such as Arylalkylamines such as Bepridil, Ditiazem, Fendiline, Gallopamil, Terodiline, Verapamil; Dihydropyridine Derivatives such as Felodipine, Isradipine, Nicardipine, Nifedipine, Nilvadipine, Nimodipine, Nisoldipine, Nitrendipine, Piperazine; Derivatives such as Flunarisine; others such as Perhexiline Calcium Regulator such as Calcifediol, Calcitonin, Calcitriol, Clodronic Acid, Dihydrotachysterol, Elcatonin, Etidronic Acid, Ipriflavone, Pamidronic Acid, Parathyroid Hormone, Teriparatide Acetate, etc.
It is to be understood herein that the active agent is intended to mean a single active agent or a combination of more than one active agent.
The amount of the systemically and/or topically active agent included in the formulation is subject to the degree to which penetration enhancement is achieved.
In the preferred embodiments, the active agents are: Amlodipine or Amlodipine Besylate presented in the compositions in about 0.05 to about 5.0 %w/w; preferably from about 0.2 to 3.0 %w/w and more preferably 0.5 to 2.0 %w/w.

2. A ternary vehicle composite comprised of a C_2-C_4 alkanol such as ethanol, isopropanol, n-propanol, butanol, preferably ethanol; a polyalcohol or glycol such as propylene glycol, butylene glycol, hexylene glycol, ethylene glycol, preferably propylene glycol and finally purified water. The compositions in accordance with the present invention contain an alcohol, preferably ethanol, in an amount of about 5.0 to about 75.0 %w/w; preferably from about 15.0 % to about 65.0 %w/w and more preferably 20.0 to 55.0 %w/w. In addition, the compositions of the present invention comprises a glycol, preferably propylene glycol in about 0.5 to about 50.0 %w/w; preferably from about 3.0 to 20.0 %w/w and more preferably 4.0 to 10.0 %w/w.

3. A permeation enhancer system comprising of a first component that is a saturated fatty alcohol given by the formula CH_3-$(CH_2)_n$-CH_2OH, in which n is an integer from 8 to 12, most preferably 10; and also a second component that is a monoalkyl ether of diethylene glycol, preferably diethylene glycol monoethyl ether or diethylene glycol monomethyl. The compositions in accordance with the present invention contain a fatty alcohol, preferably lauryl alcohol or dodecanol in about 0.1 to about 20.0 %w/w on the whole composition; preferably form about 0.4 to 10.0 %w/w and more preferably 0.2 to 3.0 %w/w; and, optionally, a diethylene glycol monoalkyl ether in amount up to 40.0 %w/w; preferably from about 0.2 to 25.0 %w/w and more preferably 2.0 to 8.0 %w/w.

4. A gelling agent or viscosant, e.g. carbomer, carboxyethylene or polyacrylic acid such as Carbopol 980 or 940 NF, 981 or 941 NF, 1382 or 1342 NF, 5984 or 934 NF, ETD 2020, 2050, 934P NF, 971P NF, 974P NF, Noveon AA-1 USP, etc; cellulose derivatives such as ethylcellulose, hydroxypropylmethylcellulose (HPMC), ethylhydroxyethylcellulose (EHEC), carboxymethylcellulose (CMC), hydroxypropylcellulose (HPC) (Klucel different grades), hydroxyethylcellulose (HEC) (Natrosol grades), HPMCP 55, Methocel grades, etc; natural gums such as arabic, xanthan, guar gums, alginates, etc; polyvinylpyrrolidone derivatives such as Kollidon grades; polyoxyethylene polyoxypropylene copolymers such as Lutrol F grades 68, 127, etc; others like chitosan, polyvinyl alcohols, pectins; veegun grades, etc. In the present invention, Lutrol F grades and Carbopol grades were preferred. Those of the skill in the art should know of other gelling agents or viscosants that are suitable to practice the present invention. Suitable gelling agents to apply the present invention include, but are not limited to, Carbopol 980 NF, Lutrol F 127, Lutrol F 68 and Noveon AA-1 USP. The gelling agent is present from about 0.2 to about 30.0 %w/w depending on the type of polymer.

5. A pH regulator, normally a neutralizant agent, which can optionally have crosslinking function e.g. a ternary amine such as triethanolamine, tromethamine, tetrahydroxypropylethylendiamine, etc; NaOH solution, etc. The pH regulator is present in the formulations in about 0.05 to about 2.0 %w/w.

6. Other ingredients can optionally be included, for example, preservatives and/or antioxidants such as buthylhydroxytoluene, buthylhydroxyanisole, ethylenediaminetetraacetic acid and its sodium salts, DL-alfa tocoferol, antioxidant complexes, etc; co-solvents or solubilizers such as glycerol, polyethylene glycols, polyethylene glycols derivatives, polyethyleneglycol 660 hydroxystearate (Solutol HS 15 from Basf), buthylene glycol, hexylene glycol, etc.

[0040] The formulations in which the present invention could be added, assume any of a variety of dosage forms. Examples are gels, creams, lotions, sprays, ointments, aerosols, patches, buccal and sublingual tablets, suppositories, vaginal dosage forms and different passive or/and active transdermal devices for absorption through the skin or mucosa.

[0041] As such, in another aspect, the present invention relates to a method for administering topically or systemically active agent(s), comprising: 1. An active agent(s) as previously defined; 2. A ternary vehicle composite (composed by a C1-C4 alkanol, a glycol and water); 3. A penetration enhancers combination (fatty alcohol and diethylene glycol monoethyl ether); 4. A gelling agent and 5. A pH regulator.

[0042] It has been discovered that in a transdermal formulation comprising different group of drugs as active agents as previously defined; lauryl alcohol and diethylene glycol monoethyl ether as penetration enhancers, in a ternary vehicle composite comprised of ethanol, propylene glycol and purified water, using a polymer or copolymer of acrylic acid, preferably a carbomer as gelling forming, provides therapeutically effective serum concentration of each active agent throughout at least a 24 hours period. As it is concluded when a bioavailability study of the above mentioned formulations were carried out in human beings volunteers.

[0043] The main aim followed by the present invention is to rapidly create a high concentration of the drug(s) in contact with the skin or mucosa attained by the careful combination of permeation enhancers and vehicles.

[0044] It is well known by the skills in the art that a sumatory or a sinergistic effect could be expected when two or more penetration enhancers are combined and included into a formulation. However, it is by no mean obvious to obtain an adequate penetration enhancement factor and a sustained flux of the active agent(s), achieving therapeutic effective levels, also controlled and sustained, by only one daily application of the formulation.

[0045] Accordingly, we can postulate that the behavior of our formulation was due to the addition of several phenomena especially on the stratum corneum.

[0046] Although the mechanism of such stratum corneum effect in the present invention is not fully clear by the scientific knowledge up to now, it can be understood as follows:

[0047] The fatty alcohol is mainly distributed to the stratum corneum because of its lipophilicity and interacts with the stratum corneum lipids.

[0048] The diethylene glycol monoethyl ether dissolves both an hydrophilic and a lipophilic active agents therein and facilitates the penetration of the active agents to the skin.

[0049] An alkanol, such as ethanol, also has a function to increase the stratum corneum liquid fluidity or a function to extract lipids from me stratum corneum.

[0050] Propylene glycol, a widespread pharmaceutical vehicle, acts as a cosolvent of the drugs hence increase the solubility of the active agent in the formulation and solvated the intracellular keratin of the stratum corneum and thus enhanced drug mobility and skin hydration.

[0051] Water serves to augment the solubility of a hydrophilic active agent in the formulation and accelerates the release of lipophilic active agent from a formulation.

[0052] A polymer or copolymer of acrylic acid, such as a carbomer acts as a gelling forming and facilitates the release of lipophilic active agent and penetration enhancer.

[0053] A tertiary amine, such as triethanolamine or trolamine, has the function to thicken and neutralize the system.

[0054] In the preferred embodiment of the present invention, the active agents and the compounds which enhances

their penetration rate (lauryl alcohol and diethylene glycol monoethyl ether) are dissolved in a ternary vehicle composite integrated by an alkanol having 1-4 C atoms, preferably ethanol; a polyalcohol, preferably propylene glycol and purified water.

[0055] This invention relates to a novel composition for transdermal or transmucosal application to humans in an optimized dosage form and methods for providing therefrom a controlled and sustained administration of the different drugs defined above.

DEFINITION OF TERMS

[0056] "Penetration enhancement" or "permeation enhancement" as used herein relates to an increase in the permeability of skin to a pharmacologically active agent, i.e., so as to increase the rate at which the drug permeates through the skin and enters the bloodstream. The enhanced permeation effected through the use of such enhancers, and in particular, through the use of the enhancer composition of the present invention, can be observed by measuring the rate of diffusion of drug through animal or human skin using a diffusion cell apparatus as described in the examples herein.

[0057] An "effective" or an "adequate" permeation enhancer as used herein means a permeation enhancer that will provide the desired increase in skin permeability and correspondingly, the desired depth of penetration, rate of administration, and amount of drug delivered.

[0058] By "transdermal" delivery, applicants intend to include both transdermal (or "percutaneous") and transmucosal administration, i.e., delivery by passage of a drug through the skin or mucosal tissue and into the bloodstream.

[0059] "Carriers" or "vehicles" as used herein refer to carrier materials suitable for transdermal drug administration, and include any such materials known in the art, e.g., any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non toxic and which does not interact with other components of the composition in a deleterious manner. Examples of suitable vehicles for use herein include water, alcohols, polyalcohols, and glycols.

[0060] By "controlled" is meant reduce or minimize peak and valley normally present in some routes of administration of a pharmacologically active agent.

[0061] By "sustained" is meant extended maintenance of steady state plasma levels.

[0062] By "therapeutically effective" amount of a pharmacologically active agent is meant sufficient amount of a compound to provide the desired therapeutic effect, avoiding high or low plasmatic levels, obtaining, therefore, plasmatic levels of active within the therapeutic window.

EXAMPLES

[0063] In order to further illustrate the present invention and the advantages thereof, the following specific examples are given. It being understood that the examples herein disclosed are intended only as illustrative and in nowise limitative.

[0064] All the examples were prepared basically. as follow: an aqueous phase (dispersion of the carbomer in water) and an alcoholic phase (solution containing the active drugs, Lauryl Alcohol, Diethylene glycol monoethyl ether (Transcutol P), and Ethyl Alcohol, or some of them according to the formulation) were prepared separately. The Propylene Glycol and Disodium EDTA, were added to the aqueous phase after the carbomer dispersion. Finally, aqueous and alcoholic phases were mixed and Triethanolamine was added to neutralize the carbomer and form the gel. The exemption was gels containing Hydroxypropyl Cellulose, which were manufactured by dispersing the Hydroxypropyl Cellulose in the hydroalcoholic solution containing the rest of the components.

[0065] The solutions were prepared by dissolving the active drugs in the rest of the excipients and shaking up to total dissolution.

[0066] The active substances included in the different formulations used in the examples or referred to in tables and graphics are defined through the following list of initials:

LNEg = Levonorgestrel + Estradiol gel
Tg = Testosterone gel
NEg = Norethindrone Acetate + Estradiol gel
Pg = Progesterone gel
EELNg = Ethynil Estradiol + Levonorgestrel gel
Alg = Alprazolam gel
T4s = L-Thyroxine solution
T4g = L-Thyroxine gel
Alps = Alprazolam solution
TEg = Testosterone + Estradiol gel
Ams = Amlodipine solution
AmBss = Amlodipine Besylate solution

[0067] Then, a numbering that represents different formulations with the same active drug (s) and same dosage form follows the initials.

Example 36(Ams001-01)

[0068] A solution composed by Amlodipine base 1.00 % w/w, Propylene Glycol 99.00 % w/w, was prepared according to the manufacturing technique herein described.

Example 37(AmBss001-01)

[0069] A solution composed by Amlodipine Besylate 1.00 % w/w, Propylene Glycol 99.00 % w/w, was prepared according to the manufacturing technique herein described.

Example 38(Ams002-01)

[0070] A solution composed by Amlodipine base 1.00 % w/w, Lauryl Alcohol 2.06 % w/w, Diethylene glycol monoethyl ether (Transcutol P) 5.15 % w/w, Propylene Glycol 91.79 % w/w, was prepared according to the manufacturing technique herein described.

Example 39(AmBss002-01)

[0071] A solution composed by Amlodipine Besylate 1.00 % w/w, Lauryl Alcohol 2.07 % w/w, Diethylene glycol monoethyl ether (Transcutol P) 5.15 % w/w, Propylene Glycol 91.78 % w/w, was prepared according to the manufacturing technique herein described.

IN VITRO DRUG PERMEATION STUDIES AND *IN VIVO* BIOAVAILABILITY STUDIES

[0072] *In vitro* drug permeation experiments through abdominal guinea pig skin were made using the diffusion chamber that is schematically shown in Figure 1 (Franz Vertical Diffusion Cell).

[0073] Female Guinea pigs, 8 to 16 months of age, were shaved on their abdominal skin 72 hours before sacrificing by cervical dislocation. Only animals that shown absence of lesions were used. A section of full thickness abdominal skin, was surgically excised and mounted between the sections of a vertical diffusion cell having 1.77 sqcm of surface area, the epidermal facing up. A given amount of the transdermal devices exemplified previously (10, 25, 50 or 400 mg or 2, 3 ml) was applied over the epidermal layer whilst the dermal layer contact with the receptor solution: 2.0 %w/V polyoxyethylene 20 oleyl ether (Oleth 20), with or without PBS, pH 7,4. The receptor chamber was maintained at 35°C and the studies were conducted under occlusive or non-occlusive conditions and at 600 rpm of stirring speed. At given time points, samples were withdrawn from the receptor solution and the receptor chamber was immediately refilled with fresh solution. All samples were analyzed using a high performance liquid chromatography (HIPLC) method.

[0074] Flux determination: Transdermal flux (mcg/sqcm/h) was determined from the steady-state slope of the plot of the cumulative amount of the drug(s) permeated through the skin versus time. After steady-state had been established, the linear portion of the plot was used to calculate the flux from the slope.

[0075] In order to demonstrate the improvements in the permeation performance applying the invention herein discloses, *in vitro* permeation studies of examples using the inventive means were compared with examples made without using this invention (without the addition of permeation enhancers).

[0076] It was an objective to demonstrate the results obtained applying the invention herein disclose. In the *in vitro* drug permeation studies the examples using the invention herein claimed were compared with examples made without using this invention (without addition of the permeation enhancers). Also, with some active drugs of the exemplified groups, comparative *in vitro* permeation studies were done against a reference product, *Combi Gel™* NETA (Estradiol + Norethindrone Acetate). Such a product has extensively tested in several human pharmacokinetic studies (Proceed. Int'1 Symp. Control. Rel. Bioact. Mater., 25, CRS, Inc. poster # 5513, 5514 and Proceed. Int'1 Symp. Control. Rel. Bioact. Mater., 26, CRS, Inc, poster #5160). Therefore, the comparative *in vitro* results allow us to consistently predict the in vivo plasmatic level profile for other active agents. Furthermore, preliminary bioavailability studies were carried out for several formulations containing the present invention. *Combi Gel™* is a trademark comprising the invention claimed herein, that means the combination of penetration enhancers.

[0077] To further exemplify the invention herein describe, a sorting in groups of active drugs was made, describing in each case the most relevant *in vitro* and in vivo results that support the present' invention. Tables and graphics illustrate the results obtained, furthermore, in vivo studies protocols and the corresponding results obtained are disclosed.

ANTIHYPERTENSIVES/CALCIUM CHANNEL BLOCKERS

Combi Gel™ Amlodipine

[0078]

A) In vitro permeation studies were performed in order to evaluate the influence of the addition of the invention means, on Amlodipine Besylate and Amlodipine (base form) permeation profile. Thus, solutions of the active drugs, with and without the addition of the invention means, were *in vitro* tested.

Study conditions: Franz Vertical Diffusion Cells (Hanson Research Inc.); Pre-shaved abdominal Guinea pig skin was used as experimental model. The receptor solution was 2 % w/w polyoxyethylene 20 oleyl ether (Oleth 20), PBS 10mM, pH 7.4. The experiments were conducted under occlusive conditions, at 35°C and 600 rpm of stirring speed. 3 ml of each formulation was loaded per cell. One sample of receptor solution was taken at different time points.

Results

Table XXX

Amlodipine and Amlodipine Besylate in vitro permeation Cumulative Amounts *(μg/cm²), Mean±SD*				
Time (h)	Example 39 (AmBss002-01) (1)	Example 37 (AmBss001-01) (2)	Example 38 (Ams002-01) (3)	Example 36 (Ams001-01) (4)
0	0.00	0.00	0.00	0.00
24	44.61 *± 18.59*	0.54 *± 0.10*	1963.13 *± 588. 62*	4.35 *±1.51*
(1) Contains 1,00% w/w of Amlodipine Besylate with the additon of the invention means (2) Contains 1,00% w/w of Amlodipine Besylate without the invention means (3) Contains 1,00% w/w of Amlodipine with addition of the invention means (4) Contains 1,00% w/w of Amlodipine without the invention means				

These results clearly shown a very significant increment in the cumulative amount permeated of both Amlodipine forms (base and Besylate) when the invention is present in the formulation (about 85 times for the Besylate and more than 450 times for the base). The enhancement effect is clearly greater for the base form.

Then, we can conclude that a formulation to administer the antihypertensive agent at an adequate permeation rate could be achieved by using the present invention.

Claims

1. Pharmaceutical composition suitable for transdermal or transmucosal administration, in form of a gel or a solution, comprising an antihypertensive active agent, as a permeation enhancers a combination of:

   a) saturated fatty alcohol of formula CH_3-$(CH_2)_n$-CH_2OH wherein n is an integer number 8 ÷ 12, most preferably 10,
   b) a ternary vehicle or carrier consisting of a C_1 ÷ C_4 alkanol, a polyalcohol in particular propylenglycol and water,
   c) a monoalkylether of diethylenglycol.

2. Pharmaceutical composition according to claim 1, wherein:

   - the component a) is in amount comprised between 0.1% and 20% by weight (preferably 0.2 + 3%),
   - the component b) comprises 5% + 75% by weight of alkanol on the whole composition and 0.5% + 50% of a glycol,
   - the component c) is in amount up to 40% by weight (preferably 2 + 8%),

3. Pharmaceutical composition according to claim 1 or 2 in form of gel, comprising, as gelling agent:

   - a polyacrylic acid such as carbopol
   - a cellulose derivative such as hydroxypropylmethylcellulose, carboxymethylcellulose, ethylhydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose

- polyvinylpyrrolidone
- polyoxyethylene/polyoxypropylene copolymers
- Polyvinylalcohol
- natural gums, alginates, pectins.

4. Pharmaceutical composition according to claim 3 wherein the amount of gelling agent is comprised between 0.2 and 30% by weight.

Patentansprüche

1. Pharmazeutische Zusammensetzung geeignet für die transdermale oder transmukosale Verabreichung in der Form eines Gels oder einer Lösung enthaltend einen blutdrucksenkenden Wirkstoff und als einen Permeationsverstärker eine Kombination aus:

   a) gesättigtem Fettalkohol der Formel CH_3-$(CH_2)_n$-CH_2OH, worin n eine ganze Zahl zwischen 8 und 12 und höchst bevorzugt von 10 ist,
   b) einem ternärem Vehikel oder Träger bestehend aus einem C_1-C_4-Alkohol, einem Polyalkohol, insbesondere Propylenglykol und Wasser,
   c) einem Monoalkylether von Diethylenglykol.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei:

   - die Komponente a) in einer Menge zwischen 0,1 % und 20 Gew.-% (vorzugsweise 0,2 bis 3 %) enthalten ist,
   - die Komponente b) 5 % bis 75 Gew.-% eines Alkanols bezogen auf die Gesamtzusammensetzung und 0,5 % bis 50 % eines Glykols enthält,
   - die Komponente c) in einer Menge von bis zu 40 Gew.-% (vorzugsweise 2 bis 8 %) vorliegt.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2 in der Form eines Gels enthaltend als Geliermittel:

   - eine Polyacrylsäure, wie beispielsweise Carbopol,
   - ein Cellulosederivat, wie Hydroxypropylmethylcellulose, Carboxymethylcellulose, Ethylhydroxyethylcellulose, Hydroxypropylcellulose, Hydroxyethylcellulose,
   - Polyvinylpyrrolidon
   - Polyoxyethylen-/Polyoxypropylen-Copolymere
   - Polyvinylalkohol
   - natürliche Gummis, Alginate, Pektine.

4. Pharmazeutische Zusammensetzung nach Anspruch 3, wobei die Menge des Geliermittels zwischen 0,2 und 30 Gew.-% beträgt.

Revendications

1. Composition pharmaceutique appropriée pour une administration transdermique ou transmuqueuse sous la forme d'un gel ou d'une solution comprenant un agent actif contre l'hypertension, comme agent améliorant la perméation, une combinaison de:

   a) un alcool gras saturé de la formule CH_3-$(CH_2)_n$-CH_2OH, où n est un nombre entier de 8 à 12, mieux de 10,
   b) un véhicule ou support ternaire consistant en un alcanol C_1 à C_4, un polyalcool en particulier du propylèneglycol et de l'eau,
   c) du monoalkyléther de diéthylèneglycol.

2. Composition pharmaceutique selon la revendication 1, où:

   - le composant a) est en une quantité comprise entre 0,1% et 20% en poids (de préférence 0,2 à 3%),
   - le composant b) comprend 5% à 75% en poids d'alcanol sur la composition totale et 0,5% à 50% d'un glycol,
   - le composant c) est en une quantité pouvant atteindre 40% en poids (de préférence 2 à 8%).

3. Composition pharmaceutique selon la revendication 1 ou 2 sous la forme d'un gel comprenant, comme agent gélifiant:

- un acide polyacrylique comme du carpobol
- un dérivé de cellulose tel que l'hydroxypropylméthylcellulose, la carboxyméthylcellulose, l'éthylhydroxyéthylcellose, l'hydroxypropylcellulose, l'hydroxyéthylcellulose
- de la polyvinylpyrrolidone
- des copolymères de polyoxyéthylène/polyoxypropylène
- de l'alcool polyvinylique
- des gommes naturelles, des alginates, des pectines.

4. Composition pharmaceutique selon la revendication 3, où la quantité de l'agent gélifiant est comprise entre 0,2 et 30% en poids.

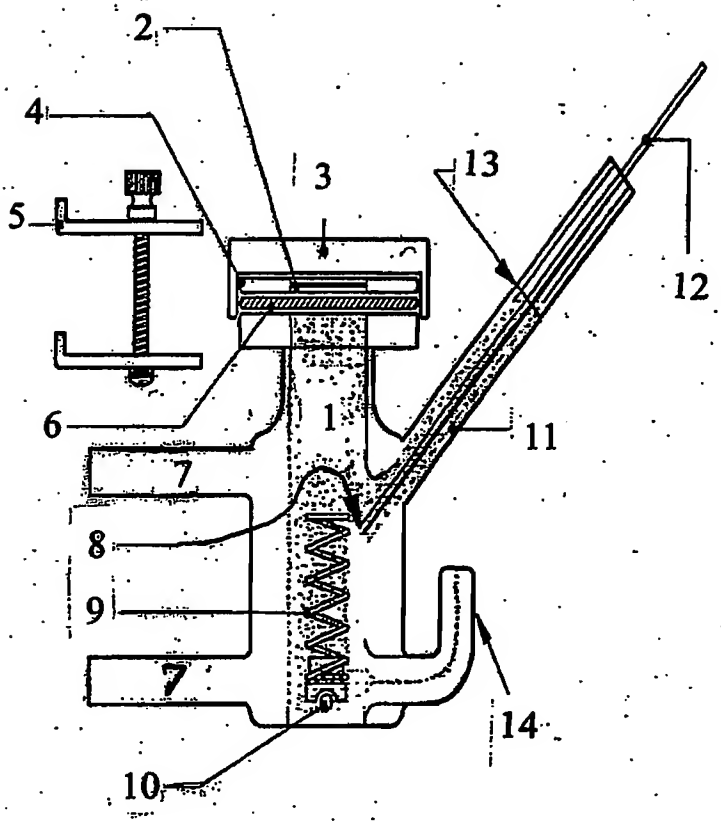
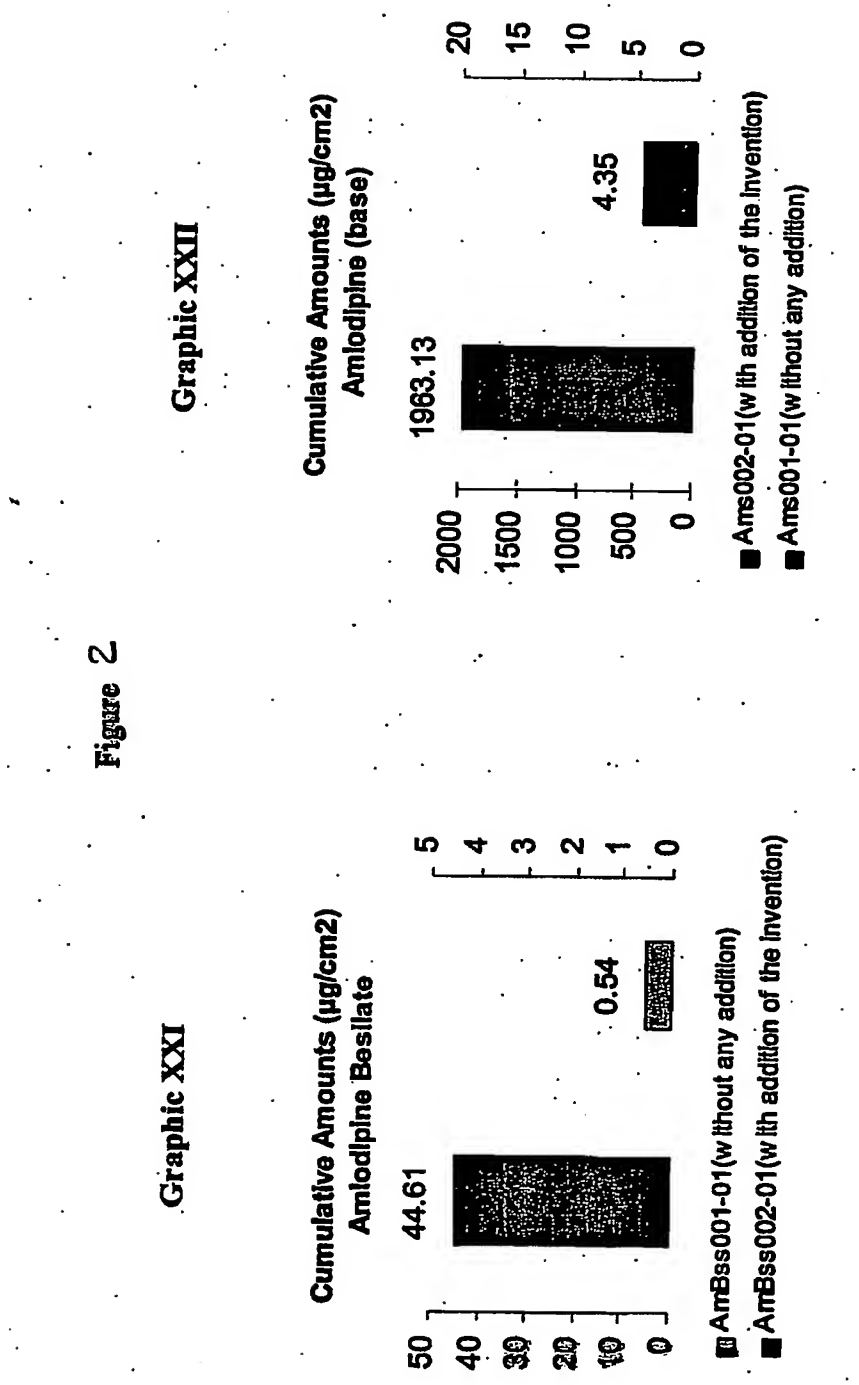


Figure 1

Figure 2


Graphic XXI
Cumulative Amounts (µg/cm2)
Amlodipine Besilate
44.61
0.54
50
40
30
20
10
0
5
4
3
2
1
0
AmBss001-01(without any addition)
AmBss002-01(with addition of the invention)
Graphic XXII
Cumulative Amounts (µg/cm2)
Amlodipine (base)
1963.13
4.35
2000
1500
1000
500
0
20
15
10
5
0
Ams002-01(with addition of the invention)
Ams001-01(without any addition)